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Survival With Combined Modality Therapy After Intracerebral Recurrence of Pleuropulmonary Blastoma

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Background. We present and discuss the successful treatment of pleuropulmonary blastoma metastatic to the brain using a multimodality regimen with surgery, high-dose chemotherapy and radiation therapy.

Procedure. A 3-year-old boy referred to our institution with bilateral pulmonary cysts was diagnosed with pleuropulmonary blastoma (PPB). Initial treatment included surgery and multiagent chemotherapy with vincristine, dactinomycin, cyclophosphamide, cisplatin, and doxorubicin. One year after the completion of therapy, his PPB recurred as an intracerebral metastasis, and required further treatment with a multimodality salvage regimen. The child was successfully treated with a subtotal surgical resection, followed by high-dose cyclophosphamide, and radiation therapy. He is now disease-free 24 months later.

Results. Intracerebral metastases of PPB have been a uniformly fatal complication of this tumor. Postsurgical chemotherapy and radiation therapy appear to have contributed to the prolonged survival and potential for cure in our patient.

Conclusions. The use of this multimodality regimen may be warranted in other patients with recurrent PPB metastatic to the brain. Med. Pediatr. Oncol. 30:63–66, 1998.

Key words: pleuropulmonary blastoma; chemotherapy; high-dose cyclophosphamide

INTRODUCTION

Pleuropulmonary blastoma (PPB) is a rare and highly aggressive pulmonary neoplasm in children. In general, most intrathoracic malignancies in pediatric patients result from metastatic spread from other more common childhood solid tumors. Pleuropulmonary blastoma of childhood exhibits unique histological, biological and clinical characteristics, and needs to be differentiated from the classic adult-type of pulmonary blastomas. The prognosis associated with PPB is uniformly poor. Histologically, these tumors have blastematous characteristics with absence of a malignant epithelial component, and in some cases, evidence of differentiation toward specific mesenchymal lines [1]. These tumors show lack of staining for p53 and MDM2 proteins, which are commonly seen in bronchogenic carcinoma and adult pulmonary blastomas [2]. The high incidence of other associated serious childhood conditions within families of patients with PPB suggests this rare tumor may be a marker for familial disease [3]. Many cases of PPB occur in patients with preexisting cystic lung disease, and common metastatic sites include lymph nodes, liver, pancreas, kidney, adrenals, and bone [1,4]. Brain metastases, uncommon in most solid childhood tumors, are also frequently observed in patients with PPB and are associated with a particularly poor outcome. We describe a case of PPB successfully treated with a combined modality regimen after the development of intracerebral tumor recurrence.

HISTORY AND THERAPY

A 3-year-old boy was referred to our institution with history of fever, cough, and tachypnea. He had been treated for several weeks for a presumed respiratory tract infection without improvement. At age 18 months he had been diagnosed with bilateral pulmonary cysts. Family history was remarkable for malignant brain tumor in maternal grandfather, and malignant melanoma in maternal grandmother and great-grandmother. Physical examination revealed decreased breath sounds in the left hemithorax. A CT scan of the chest showed a left lower lobe mass, small pneumothorax and a contralateral lung cyst (Fig. 1A). Excisional biopsy of the mass was diagnostic of pleuropulmonary blastoma (Fig. 1B). Metastatic work-up was negative. He was treated with four cycles of cisplatin 20 mg/m^2/day (days 1–5), doxorubicin 25 mg/m^2/day (days 1–3), and vincristine 1.5 mg/m^2/day (days 1 and 7), alternating with four cycles of cyclophospha-

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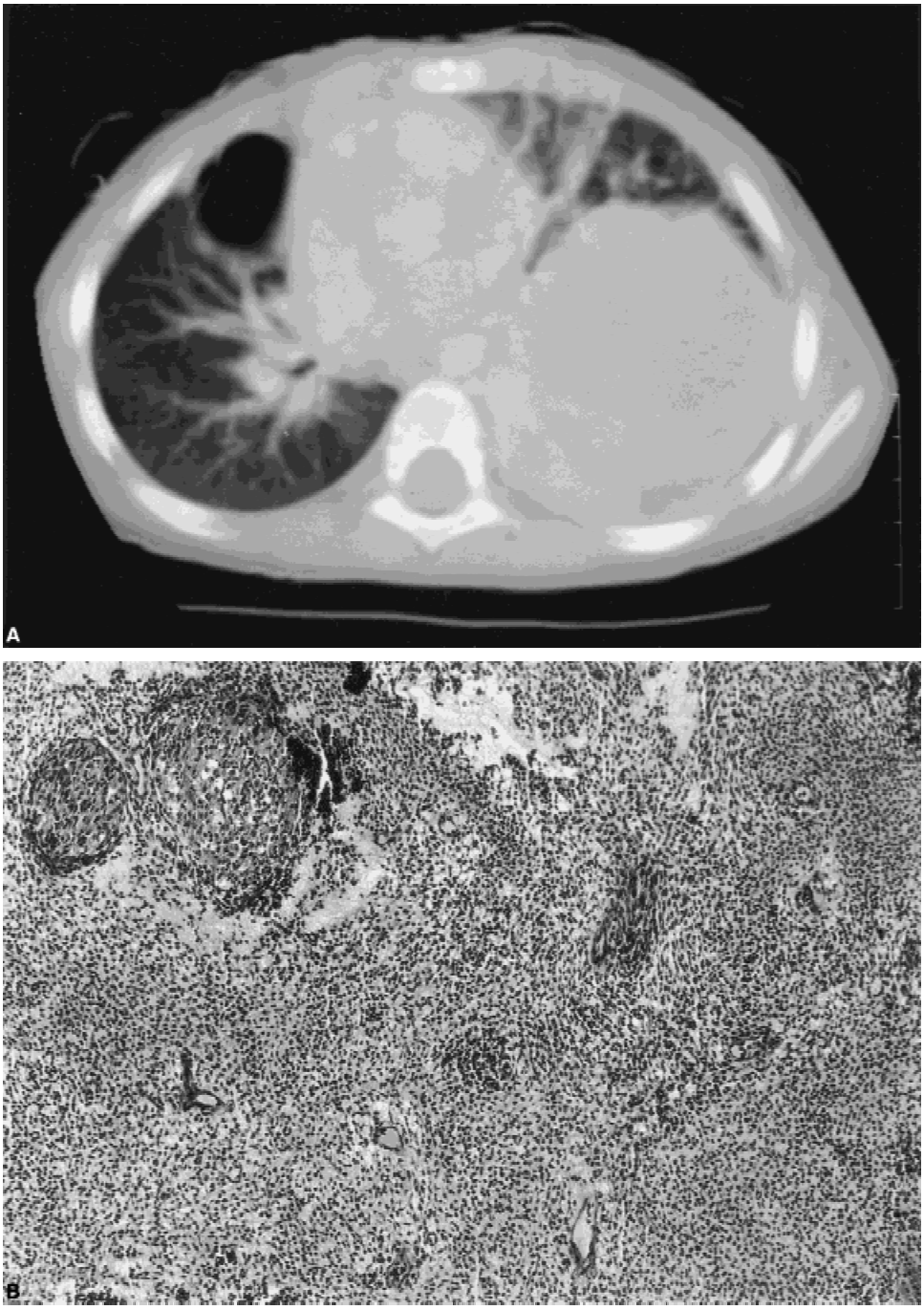

Fig. 1. **A:** Computer tomography of the chest at initial diagnosis demonstrates large left pulmonary mass with small pneumothorax above the mass, and presence of contralateral cystic lesion. **B:** Photomicrograph of the primary lung lesion showing densely cellular areas with mesenchymal and blastematous tissue elements, cartilaginous differentiation, and areas of necrosis. Other areas of the tumor display stellate and spindled embryonic stroma arranged in linear and whorling patterns. Embryonic cellular component is generally undifferentiated.

mide (CTX) 300 mg/m^2/day (days 1–3) and dactinomycin 20 mcg/kg/day (days 1–4).

One year after completion of therapy, he developed headaches and vomiting. A CT scan of the brain showed a large frontal lobe mass (Fig. 2A). During surgical exploration, fragments of a large, necrotic, friable right frontal brain mass were removed by gentle suction and irrigation. No distinct tumor capsule was identified. Histology was consistent with metastatic PPB, and margins were positive for tumor (Fig. 2B). Postoperative CT scan showed residual enhancing ring at the tumor site. He was treated with four cycles of high-dose CTX 2 g/m^2 × two

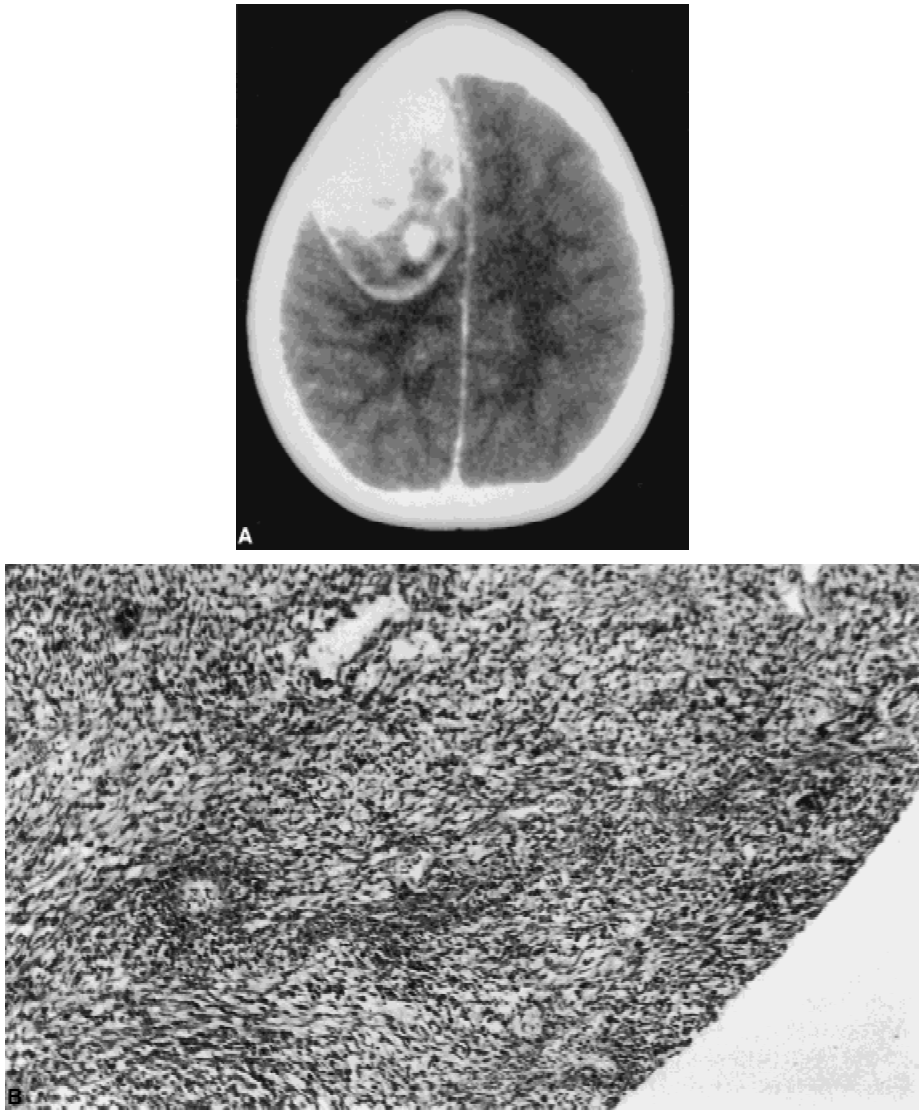

Fig. 2. **A:** CT scan of the brain at time of tumor recurrence showing a large enhancing lesion in the right frontal lobe, associated surrounding vasogenic edema and midline shift. **B:** Photomicrograph of the metastatic brain lesion showing a densely cellular area showing undifferentiated mesenchymal cells. There is no identifiable tumor capsule and surgical margin shows infiltration by tumor cells.

consecutive days followed by GM-CSF 250 mcg/m^2 BID, and whole brain radiation (3,000 cGY) in 12 fractions. He is now 24 months off therapy without any evidence of disease.

DISCUSSION

Pleuropulmonary blastoma is a rare embryonic tumor of the lung generally seen in children under the age of 16 years. It was first described by Barrett and Barnard in 1945 as lung embryoma due to its histological resemblance to fetal lung [5]. Spencer in 1961 introduced the term pulmonary blastoma because of the concept of it arising from the pulmonary blastema, in the same way Wilms' tumor arises from the renal blastema [6]. More recently, PPB of childhood has been established as distinct from the classic adult-type pulmonary blastoma seen mostly in patients over the age of 30 years [1]. Based on histopathological characteristics, three subtypes have been described [4]. Type 1 PPB are those presenting as thin-walled cysts, type 3 PPB are predominantly solid tumors, and type 2 tumors are those which present intermediate features between purely cystic and solid PPB. Type 1 tumors contain epithelialized cysts with septal stroma with small cells resembling those of primitive embryonal rhabdomyosarcoma. In contrast, the solid areas of type 2 and 3 PPB contain blastematous islands, nodules of cartilage with features ranging from

benign to sarcomatous, rhabdomyoblasts, and highly pleomorphic anaplastic cells. None of the PPBs described to date have contained malignant glandular or immature tubular structures seen commonly in bronchogenic carcinoma.

The clinical presentation of our patient is consistent with that of most reported cases. Typically, a nonproductive cough, chest pain and fever ranging in duration from days to weeks are the most common symptoms at presentation. Other physical complaints have included weight loss, fatigue, abdominal pain, and respiratory distress. As in our patient, the initial symptoms are many times interpreted as manifestations of a respiratory tract infection. Radiologic findings indicate the presence of cystic disease at presentation in approximately 40% of cases. Other findings include pleural effusion, pneumothorax, entire opacification of a lung field, and deviation of the mediastinum. For patients who present with cystic pulmonary lesions, the interval time to diagnosis of PPB has been delayed up to 36 months. This rare childhood tumor has been proposed to be genetically linked to other embryonal malignancies. Sciot and coworkers [7] reported cytogenetic abnormalities of 2q, similar to those described in hepatoblastoma and embryonal rhabdomyosarcoma. Further, this rare tumor has been proposed as a marker for a constitutional and heritable predisposition to dysplastic and neoplastic disease. In an analysis of 45 cases of PPB, Priest et al. [3] reported an association with familial occurrence of pulmonary cysts, cystic nephromas, sarcomas, medulloblastomas, thyroid dysplasias and neoplasias, Hodgkins disease, leukemia, and Langerhans cell histiocytosis in 12 cases (25%). These investigators were unable to pinpoint any abnormalities of the Wilms' tumor WT1 and WT2 genes, and the p53 tumor suppressor genes, consistent with the report from Pacinda et al. [2]. Thus, any molecular basis for these clinical associations remains to be determined.

The overall prognosis for children with PPB has been poor, and treatment for this tumor has been traditionally surgery alone. Both chemotherapy and radiation therapy have been used as adjuvant therapy. The frontline therapy received by our patient was similar to that reported by others [8–11]. In general, those agents known to be active against other childhood sarcomatous tumors have yielded responses in patients with PPB. The role of combination chemotherapy in these patients has been effective as initial therapy in inoperable tumors and for patients with metastatic disease. The presence of metastasis has been known to occur both at diagnosis and after cessation of initial therapy. The presence of brain metastasis in patients with PPB has been uniformly fatal in all cases reported to date [1,11–14]. At the time of relapse our patient had already been treated with most agents considered effective against PPB. Most of the agents are known substrates for the P-glycoprotein, decreasing significantly their potential effectiveness at the time of relapse. Our choice of high-dose cyclophosphamide was based on the steep dose response curve known to characterize the pharmacology of most alkylating agents, allowing for dose escalation as a successful strategy to overcome resistance. This regimen, although myelosuppressive, was well tolerated with the use of GM-CSF to minimize hematological toxicity. Radiation therapy was also included as a noncross-resistant treatment modality to high-dose single agent chemotherapy, and in order to maximize tumor response. Thus, our experience suggests that an aggressive multimodality treatment which includes surgery, high-dose chemotherapy, and radiation therapy should be attempted in patients with PPB presenting or recurring with brain metastases. This approach could also prove useful for patients presenting or recurring with metastatic PPB outside the central nervous system.

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